A STUDY OF EXTENDED LIPID LIPOPROTEIN PROFILE IN NEWLY DIAGNOSED DIABETIC AND HYPERTENSIVE PATIENTS

THESIS
FOR
DOCTOR OF MEDICINE
(INTERNAL MEDICINE)

BUNDELKHAND UNIVERSITY
JHANSI (U.P.)

2006 VINOD KUMAR SINGH

Dedicated

to my Parents

CERTIFICATE

This is to certify that the work entitled "*A study of extended lipid lipoprotein profile in newly diagnosed diabetic and hypertensive patients*" which is being submitted as thesis for M.D. (Medicine) Examination 2006 of the Bundelkhand University, Jhansi, has been carried out by **Dr. Vinod Kumar Singh** in the Department of Medicine, M.L.B. Medical College, Jhansi.

The method described was undertaken by the candidate himself and the observations recorded have been periodically checked. He has put in the necessary stay in the department as per university regulations, and has fulfilled the conditions required for the submission of the thesis according to the University regulations.

Dated :

Place - Jhansi

Dr. P.K. Jain
M.D., MNAMS
Professor & Head,
Department of Medicine,
M.L.B. Medical College,
Jhansi

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The techniques embodied in the thesis were undertaken by the candidate himself and the observations recorded have been checked and verified by me from time to time.

Dated :

Place - Jhansi

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Vinod kumar singh

Date : 26/10/2008 *Dr. Vinod Kumar Singh*

CONTENTS

Introduction

INTRODUCTION

Diabetes mellitus (DM) comprises a group of common metabolic disorder that share the phenotype of hyperglycemia. Diabetes mellitus is the most prevalent metabolic non communicable disorder in the world. The Increasing prevalence of type II diabetes mellitus is a global problem, and it is unfortunately, a major one in developing countries such as India. The world presently has nearly 150 million diabetes of which one fifth that is approximately 33 million are in India. This number is predicted to double by 2025. In fact India has been dubbed as a diabetes capital of the world at the recent 2003 International diabetes federation (IDF) conference in Paris (1).

Diabetes mellitus has emerged a major public Health problem in our country and has assumed epidemic proportions. Prevalence of diabetes has increased form 2.1 % in 1972 to almost 20% in 2003. The vast majority of these are type 2 patients.

Most of the diabetes develop micro and macrovascular complications of it, manifesting as cardiovascular disease cerebro-vascular disease, renal disease, peripheral vascular

disease etc. Cardiovascular disease is presently the leading cause of death among person with diabetes (2). Dyslipidemia is one of the major risk factor for cardiovascular disease and is also very common in both individuals with type I and type II.

Dyslipidemia is a state in which circulating levels of lipids or lipoprotein fractions are abnormal because of genetic and/or environmental conditions that alter the production, catabolism or clearance of plasma lipoproteins. An understanding of lipoprotein metabolism is of particular importance because of association of lipoproteins with coronary heart disease, one of the leading cause of mortality in today's world (30% of total deaths).

Abnormalities in lipoproteins are very common in both individuals with type II and those with type I. Although lipoprotein alterations appear to be intrinsic part of these disorders such alterations also are induced by diabetes - associated complications such as obesity and renal disease.

Dyslipidemia in Type I Diabetes:

A Spectrum of situations are possible in type I, from Insulin deficient ketoacidotic state with greatly elevated glucose, Free Fatty acids, ketones and lipolytic enzymes such as glucogon and

epinephrine, to a state of continuous insulin infusion therapy with hyperinsulinemia, normal or close to normal glucose and Fatty acids level. The lipid profile was near normal in well controlled type I diabetes.

In untreated type I diabetics the fractional catabolic rate for triglyceride decreased because the activity of lipoprotein lipase is dependent on insulin and leads to hypertriglyceridemia (3). Some times severe enough to cause lipaemia retinalis, acute pancreatitis and eruptive xanthomas.

VLDL (C) levels are greatly elevated in individuals indiabetic ketoacidotic state (4). LDL (C) levels are increased in poorly controlled type I subjects. LDL fractional clearance is probably decreased in poorly controlled type I individuals because insulin potentiates LDL binding to its receptors.

The LDL particles of individuals with type I may exhibit an increase in the ratio of cholesterol to Apo - B (5). In addition glycation of the LDL also interferes with the clearance of it.

A number of studies have shown that HDL-C concentrations are low in poorly controlled type I individuals and it increased with the degree of glycemic control. But some

studies have shown that HDL-C concentration in type I. inciduals are higher or not lower than the control subjects. Low lipoprotein lipase activity may be an important for lowered HDL-C concentrations in type I subjects. Adequate control of plasma glucose in type I individuals leads to increase in the HDL-C levels (6,7).

Type II diabetes mellitus causes A charateristic Dyslipidemia

Triglycerides and very low density lipoprotein cholesterol (VLDL-C). The most common alteration of lipoprotein in type II is hypertriglyceridemia caused by an elevation in VLDL-C. The most important factor responsible for increased VLDL level is over production of VLDL triglyceride probably due to increase flow of substrates such as glucose and Free Fatty acids to the liver. In addition individuals with type II have defect in clearance of VLDL triglycerides. Due to decreased lipoprotein lipase activity which parallels to the insulin resistance, thus in turn to hyperglycemia.

Low density lipoprotein-cholesterol (LDL-C): - studies examining plasma concentration of total cholesterol and LDL-C in type II have been contradictory with some showing higher and showing lower levels in type II than in control subjects. But the

recent study II of the National Health and Nutrition Examination Survey, USA, indicates that elevations of LDL-C concentrations are more common in individuals with type II DM that in the general population (8, 9,10).

High Density Lipoprotien: - Cholesterol (HDL-C) the individuals with type II DM have lower concentration of HDL-C as compared with control subjects because of increased clearance rate of HDL-C which is directly related with plasma glucose concentration. Since HDL-C concentration increases during lipolytic process, lipoprotein lipase activity has been shown to correlate significantly with the HDI-C concentrations in individuals with type II DM.

As with LDL and VLDL particles, an increased proportion of triglyceride in HDL particles have also been observed. An increase in the ratio of cholesterol to protein in HDL particles has been reported. These compositional changes appear to correlate with the degree of stimulation of adipose tissue lipoprotein lipase. In addition, glycation of the HDL particles appears to interfere with binding to receptors (11).

Apo-B concentration: - An elevated Apo-B concentration is

another common feature of the Dyslipidemia of type II diabetes. Elevated Apo-B levels are found in almost half of normocholesterolaemic patients with type II diabetes and are frequently associated with low HDL cholesterol levels and hypertriglyceridemia. Indeed, an increased in Apo-B levels may predict CHD events better than LDLCholesterol levels (12).

Apo-Al Concentrations: - Apo-Al is the crucial structural apoprotien for HDL. An contrast to athenogenic Apo-B lipoproteins, the Apo-Al containing HDL appear to be anti atherogenic. In fact in some studies, HDL cholesterol levels are as strong an indication of protection from CHD as LDL-cholesterol levels are an indicator of risk (13).

Lipoprotein-a :

Lipoprotein-a IS an LDL- like particle that carries the Lpa specific highly glucosylated protein Apo-a. Glycamic control and insulin therapy may influence Lp-a

level in patient with diabetes. There..is no clear evidence that Lp-a contributes significantly to the increased risk of atherosclerosis in diabetes, although diabetic nephropathy seem to be associated with high Lp-a levels. LDL cholesterol connected positively and

triglyceride negatively with Lp-a concentrations (14).

Lipoprotein level and coronary heart disease. In the past raised LDL-cholesterol levels were held largely responsible for the increased risk of CHD. But it is now clear that other lipid abnormalities, reduced HDL-cholesterol levels and increased triglyceride concentrations may be more important in diabetic patients.

Dyslipidemia and Hypertension :

Hypertension is an independent risk factor for the development of CHD as well as stroke, and does not significantly affect lipid levels. There is a synergistic risk enhancement effect of concurrent dyslipidemia and hypertension. So, every hypertensive patient should be screened for dyslipidemia.

Review of Literature

REVIEW OF LITERATURE

Diabetes mellitus is a syndrome characterized by disturbances of metabolism of carbohydrate, fat and protein. Fat metabolism disorder is common in both type I and type II diabetes mellitus.

SIGNIFICANCE OF DYSLIPIDEMIA IN DIABETES MELLITUS

Dyslipidemia is undoubtedly a major risk factor for coronary heart disease (CHD), about 75% of diabetics includes hypertriglyceridemia, low levels of high density lipoprotein cholesterol, small, dense, triglyceride rich low density lipoprotein particles and an increase in Apolipoprotein – B (16,17,18). Apart from these glycation and oxidation of all lipoprotein disease is enhanced.

The role of triglyceride as a cardiovascular risk factor is debatable. Most studies demonstrated increased risk of coronary heart disease (VHD) with hypertriglyceridemia with univariate analysis. (19,20,21,22). While others, taking into account other risk factors in multivariate analyses, do not (23).

In World Health Organization's cross sectional multinational study of more than 1900 persons with diabetes, Plasma triglyceride levels were significantly related to CHD, independent of other risk factors (24).

The impact of serum total cholesterol levels on CHD appears to be similar in diabetic and non diabetic individuals (25). Multiple risk factor intervention trial has shown that cardiovascular risk related to serum total cholesterol was much higher in those with diabetes than in those without diabetes at all levels of cholesterol (26).

Composition of low density lipoprotein particles in diabetes mellitus is altered, resulting into small dense, triglyceride rich particles. Although such particles have been associated with CHD in general population (27), no studies of this association in diabetes have been reported so far.

Levels of High Density Lipoprotein Cholesterol are uniformly low in untreated patients with Type I DM and Type II DM. Most studies show an association between low levels of high density lipoprotein cholesterol and CHD in both type I and Type II DM individuals (22, 28).

The Framingham study showed that High Density Lipoprotein Cholesterol levels were inversely related to CHD in diabetic population, as in the general population (29).

Thus dyslipidemia in diabetes is strongly associated with accelerated atherosclerosis which is the cause for macrovascular complications of diabetes such as cardiovascular disease, cerebrovascular disease, peripheral vascular disease.

Other lipoprotein related risk factors for CHD in diabetes mellitus include lipoprotein a [La(a)] and Apo B, Lp(a) is a unique molecule comprising a lipoprotein particle resembling LDL cholesterol that is covalently bonded to apo (a), a large plasma glycoprotein. The individual characteristics of these two components are thought to be responsible for the apparent pathogenic role of Lp(a) which has no known physiologic function. The LDL cholesterol component likely contributes to atherogenesis, where as apo(a), similar in structure to plasminogen, may promote thrombosis. Thus LP(a), which has been isolated in the arterial wall at sites of atherosclerosis, may serve as a link between the pathogenetic processes of atherosclerosis and thrombosis.

Apolipoprotein (a), large glycoprotein that shares a high degree of sequence hemology with plasminogen is made by hepatocytes and is secreted into plasma where it forms a covalent linkage with apo B 100 of LDL to form lipoprotein (a) is not known, but elevated levels are associated with an increased risk for atherosclerosis. Recent preliminary reports suggest that Lp(a) levels may be altered by glycemic control in diabetic subjects (3) and that Lp(a) level are increased in diabetic patients with either micro or macroalbuminuria (31), the alteration that may in past explain the increased CHD risk associated with proteinuria (32).

Lipoprotein (a) is an independent risk factors for coronary artery disease in NIDDM patient in South India. A article published in 1998. They reported that Lp(a) levels were significantly higher in NIDDM. Patients with CAD compared with NIDDM patients without CAD and control subjects. In NIDDM patients with CAD, there was no correlation between Lp(a) and serum cholesterol, Triglyceride, or HDL cholesterol levels, but there was a weak association with LDL cholesterol and systolic Blood pressure (33).

SM Haffners summarize role of Lp(a) in diabetes currently :

1) Lp(a) in NIDDM : Concentration are probably elevated. Concentrations are probably related to metabolic control. Concentrations are increased with microalbuminuria.

2) Lp(a) in NIDDM : Concentration are not elevated. Concentrations do not change with metabolic control.

3) Lp(a) and CHD in diabetes: Little current evidence shows that Lp(a) is a risk factor for CHD in diabetes (34).

SM Haffner et al studies Lp(a) concentrations in NIDDM. NIDDM patients have two to four fold increased risk of CHD relative to diabetic subject. This excess risk is explain only partially by increased levels of standard risk factors. Duration of diabetes and level of fasting glycemia were not significantly higher in patients who had higher total and LDL cholesterol levels. They conclude that in a large population based study, Lp(a) levels are not increased in NIDDM patients (35).

DL rainwater, JW Lacclueer et al found that the diabetic group had significantly lower Lp(a) concentrations than the non diabetic subjects (36).

Ron C. Hoogeveen, Jasvinder K. Gambhir et al suggested that elevated plasma Lp(a) confers genetic predisposition to CHD

in Asian Indians, and nutritional and environmental factors further increase the risk of CHD. Including Lp(a) concentration and Apo(a) phenotype in screening procedures may permit early detection and preventive treatment of CHD in this population (37).

Apolipoproteins are protein moiety of a lipoprotein is known as an apolipoprotein. The apolipoproteins provide structural stability to the lipoproteins and determine the metabolic fate of the particles upon which they reside. They were names in an arbitrary alphabetical order and, for the purposes of this discussion, will be described in relation to their association with lipoprotein classes.

Apo AI, AII and A IV are found primarily on HDL. There are two forms of apoB- apo B100 and apo B48. apo B100 is the major apolipoprotein of VLDL, IDL and LDL comprising approximately 30,60 and 95% of the protein in these lipoproteins, respectively. Plasma levels of HDL cholesterol and Apo A1 are inversely related to risk for CHD.

AM Wagner, A Perez, F Calvo et al studies that hyperapo (B) was found in almost half of the normocholesterolemic type II diabetic patients and was frequently associated with low HDL-C levels and hypertrilgyceridemia. Thus, given its independent

association with cardiovascular disease and that it identifies high risk phenotypes in normocholesteralemic diabetes patients Apo-B should be used to evaluate the lipidic pattern of these patients (38).

Gonan Walldius, Ingman Jungner et al studied that Apo-B and Apo B/Apo A1 ratio were strongly and positively related to increased risk of fatal myocardial infarction in men and women. Apo A1 was noted to be protective. Apo-B was a stronger predictor of risk than LDL-cholesterol in both sexes (39).

Allan D Sniderman, MD, Thea Scantlebury et al showed that abnormalities in insulin and glucose metabolism do not seem to entirely account for the high frequency of cardiovascular disease in patients with type II diabetes mellitus. An important additional factor may be hypertriglyceridemic hyperaop-B are hyertriglyceridemia, low levels of high density lipoprotein cholesterol; and increased number of small, dense low density apoprotein cholesterol (LDL) particles (70).

H. Tineke Westerveld; Jeanine E, Roetersvan Lennep; et al showed that Apo-B, chol, LDL- chol, HDL –chol, and TG were independently related to CAD. In the lowest quartiles of chol, LDL-

chol, and TG, CAD positive women had higher apo-B concentrations than CAD negative women. In contrast, chol, LDL-chol, TG, or HDL-chol levels were not different in any quartile of apo-B. apo-B showed the most significant relation with the number of stenotic vessels, and apo-B was associated with CAD in the normolipidemic subgroup. In conclusion, apo-B was superior to chol, LDL-chol, HDL-chol, TG and Apo-A1 in discriminating between CAD positive and CAD negative (41).

Benoit Lamarche, Sital Moorjani et al showed that Apo-B may be regarded as a relevant tool in the assessment of CHD risk in men, because it may provide information that would not be obtained form the conventional lipid-lipoprotein profile (42).

Mikko Syvanne, Juhanikahri et al showed that Apo AII containing lipoproteins and HDL-3 cholesterol are powerful markers of CAD in men with NIDDM (43).

Carmine et al studied silent marker for assessment of asymptomatic coronary artery disease in apparently uncomplicated type II diabetic patients. They found high Lp(a) in CAD groups (44).

M Laaksò, Slehto et al studied the association of lipoprtein fractions with the further risk of coronary heart disease in patients with non insulin dependent diabetes, they found that low LDL and HDL, cholesterol, high VLDL chol, and high total and VLDL triglycerides are powerful risk indications for CHD events in patients with NIDDM (45).

In the past vast number of studies have shown that dyslipidemia usually in the form of increased cholesterol levels in the blood is a predisposing factor for accelerated atherosclerosis (46) altherosclerotic vascular disease is the major cause of mortality and morbidity in diabetes (47). Thus dyslipidemia in diabetics, acts as an independent factor for various diseases which occur more commonly in diabetic individuals than in non diabetics individuals such as coronary artery disease (AD), cerebrovascular disease, peripheral vascular disease etc. Framingham study (48,49) and Joslin clinic study (50) have shown that incidence of CAD in diabetic subjects is two to three times more as compared to that in non diabetic individuals. Paris prospective study (51), Tecumseh study (52) and Chicago Heart association detection project (53) have shown a relation between asymptomatic hyperglycemia and cardiovascular risk. These studies strongly

suggest that asymptomatic hyperglycemia is an independent risk factor for CAD. Tecumsch study (52) has shown that although diabetes was a statistically significant independent risk factor for mortality due to CAD, an elevate blood glucose level in those individuals without diagnosis of diabetes also was associated with increased mortality due to CAD. Chicago Heart association detection project (53) states that both diabetes and asymptomatic hyperglycemia were associated with increased mortality from CAD.

Like CAD, cerebrovascular disease is also more common in diabetic individuals than in non diabetic individuals. Polumbo PJ et al (54) and Abbott et al (55) have suggested that incidence of cerebral infarction in diabetic individuals is one and half times to two times more common than in persons without diabetes.

Framingham study (56) indicated an increased risk of cerebral infarction in individuals with an even slight intolerance to glucose.

In a community based study in Rochester Minnesota (54) the observed frequency of transient ischaemic events was three times greater than expected and the frequency of stroke was 1.7 times greater than expected among diabetic individuals.

Framingham study (56) showed that incidence of peripheral vascular disease was four times higher in women with diabetes in comparison to persons without diabetes. Relative excess of clinical atherosclerotic diseases in patients with diabetes appear to be more marked in women than in men, effectively eliminating the relative protection from atherosclerosis in non diabetic women in the middle years (57).

Most studies conducted in the past on dyslipidemia in diabetes have been conducted in context with the coronary artery disease. Multiple risk factor intervention trial had shown that at every level of cholesterol, coronary heart disease risk of diabetic individuals exceeds that of non diabetic individuals by two to three times (58).

The commonest pattern of dyslipidemia in diabetes mellitus is manifested as :-

- Elevated levels of serum triglyceride
- Low levels of serum high density lipoprotein cholesterol
- Increased non high density lipoprotein cholesterol levels (low density lipoprotein cholesterol and very low density lipoprtein cholesterol).

- Small, dense and cholesterol rich low density lipoprotein particles.

- Newer increased levels of Apo-B in normocholesterolemic patients.

This type of dyslipidemia is more prevalent among individuals with type 2 diabetes mellitus as well as in insulin resistant syndrome states as observed by Grensberg HN et al (59) and Yoshino G et al (60).

Gensberg noted that data form the Paris prospective study (61) were among the earliest to show increasing coronary heart disease mortality with progression from normal glucose tolerance to impaired glucose tolerance to diabetes mellitus. Paris prospective study also showed that hypertriglyceridemia in individuals with diabetes mellitus was an important cardiovascular risk factors, particularly in individuals with hypecholesterolemia (62).

Joglekar and coworkers studied the lipid profile in newly diagnosed type 2 patients with regard to levels of cholesterol, Triglyceride and non esterified fatty acid (NEFA). They concluded that triglyceride and NEFA were raised significantly in newly

diagnosed patients while cholesterol was not in comparison to controls (63).

In a Finish study (64), it was observed that elevated serum triglyceride levels and decreased high density lipoprotein cholesterol levels predicted coronary heart disease in well characterized way in type 2 diabetic subjects. However after adjustment of high density lipoprotein cholesterol, neither serum total cholesterol nor very low density lipoprotein cholesterol or serum triglyceride predicted coronary heart disease. On observational studies, high density lipoprotein cholesterol maybe the best predictor of coronary heart disease in type 2 diabetic subjects followed by serum triglyceride and serum total cholesterol.

Garg et al (65) showed that dyslipidemia in diabetes was characterized by high serum triglyceride levels along with high serum total cholesterol levels and low levels of high density lipoprotein cholesterol.

Similarly Huth K, et al (66) observed that the main feature of disordered lipid metabolism in diabetic individuals was hypertriglyceridemia. He did't comment on serum total cholesterol

and high density lipoprotein cholesterol. But stern MP, et al (67) observed that characteristic lipid abnormalities in type 2 diabetic subjects were hypertriglyceridemia and low levels of high density lipoprotein cholesterol but with no changes in serum total cholesterol levels. They also stated that adequate glycemic control could favourably alter lipid profiles in type 2 diabetic individuals i.e. reduction in serum triglyceride levels and a rise in high density lipoprotein cholesterol levels, but regarding cardiovascular mortality as an end point of diabetes, they observed no benefit of adequate glycemic control.

Chandalia HB, et al (68) have observed hypercholesterolemia and hypertriglyceridemia both, in individuals with type 2 diabetes. They also recommended that diet of an individual with diabetes should contain so much fat that he should get 30% of total calorie form fat and out of these 30% of total calories, 10% should be derived from each saturated fats, polyunsaturated fats and monounsaturated fats. The total cholesterol consumption should not exceed 300 mg per day. They also observed that regular exercise reduced the cholesterol and triglyceride concentrations in diabetic individuals. The effect on triglyceride was most pronounced.

Diabates Control and Complications Trial Research group (69) have observed that hypertriglyceridemia was the most prominent feature of diabetic dyslipidemia. Authors also observed that most dyslipidemias in diabetic individuals resolve within 6-8 weeks of good metabolic control. Thus they recommended that an adequate control of blood glucose with any mode of treatment, be it a sulfonylurea, biguanide, insulin or combinations of these lowered lipid levels in the blood especially triglycerides. Patients exhibiting persistent dyslipidemia despite of adequate control of blood glucose require hypolipidemic drugs.

Chan et al (70) observed that post prandial hyperlipidemia was more common in individuals with diabetes mellitus in comparison to subjects with normal glucose tolerance. They observed to that post prandial very low density lipoprotein cholesterol levels were raised while that of chylomicrons were similar when compared with the normal subjects. They suggested that this post prandial hyperlipidemia may also contribute to atherosclerotic risk in patients with diabetes.

Pandit MK, et al (71) and Lardinois CK, et al (72) observed that antihypertensive agents (Beta blockers, thiazide diuretics)

used to treat hypertension in diabetic individuals may adversely affect glucose tolerance lipid levels or both.

Gonen B, et al and Lopas- Virella MF et al observed that in Type 1 diabetics with pure diabetic dyslipidemia adequate insulin therapy often completely corrected all the diabetes associated lipid abnormalities.

Dunn F et al (73) observed that when blood glucose levels of Type 2 diabetics were adequately controlled with suffonylurea therapy, the accompanying elevated lipid levels were often reduced significantly as well but not to the desirable range insulin therapy also even when glucose was successfully controlled improved but did not normalize levels of triglycerides and other lipid subfractions in these patients (74).

Since the classic risk factors do not account for the excess risk of atherosclerosis in diabetes Syvanne M et al has proposed that dyslipidamia associated with diabetes may be the cause of accelerated atherosclerosis in Type 2 diabetes patients (75).

Kannel WB, et al (76), Taskien MR et al (77) and Howard BV et al (78), during the different studies found that in patients with Type-2 diabetes mellitus with good or fair glycemic control, the

concentrations of low density lipoprotein cholesterol were similar to or slightly lower than those of non - diabetic individuals. However they found that two abnormalities characterized lipoprotein metabolism in Type 2 diabetes patients.

1. Fasting and postprandial concentrations of triglyceride rich lipoproteins especially very low density lipoproteins were higher and.

2. Fasting and post prandial concentrations of high density lipoprotein were lower than among individuals without diabetes.

Malmstram R et al (79) suggested that insulin resistance may be the common basis for hypertriglyceridemia found in Type 2 diabetes. In the insulin resistant state there is impairment of the normal suppression of fatty acid release from adipose tissue in the postprandial state consequently there is a continuous supply of free fatty acids to the liver and overproduction of very low density lipoprotein from these substrates. Secondly acute hyperinsulinemia as seen after a meal suppresses the production of large buoyant very low density lipoprotein particles in the liver in non diabetic people but not in persons with Type 2 diabetes (79).

Nathan DM et al (80) during his epidemiological study of cardiovascular disease in type 2 diabetes mellitus, observed that apart from other risk factors such as poor glycemic control, insulin resistance, obesity, increased plasminogen activator inhibitor 1 dyslipidemia in the form of hyper triglyceridemia and small dense low density lipoprotein particles also played a major role causaiotn of cardiovascular disease in type 2 diabetic patients.

Haffner SM et al (81) has shown that despite of hypertriglyceridemia with low high density lipoprotein cholesterol levels being the most common pattern of dyslipidemia in Type 2 diabetic individuals, the median triglyceride level in Type 2 diabetic individuals was less than 200 mg/dl and85-95% of Type 2 diabetic patients have triglyceride levels below 400 mg/dl.

Pan XR et al (82) have shown that dyslipidemia among Asian diabetic subjects is not so prominent and their triglyceride and high density lipoprotein cholesterol levels are comparable to those of Western non diabetics.

UKPDS 27 (83) observed that the effect of NIDDM on plasma lipid and lipoprotein levels is more pronounced in women

than in men. This may explain in past why the cardiovascular risk is proportionally higher in females.

M. Uusitupa, O Siitonen et al (84) studied serum lipids and lipoproteins in newly diagnosed type II diabetic patients. They found that the serum total cholesterol levels in diabetic and non diabetic subjects were similar, but the HDL cholesterol levels were lower and the serum total triglyceride levels higher in the diabetic than in non diabetic subjects. No significant differences were found in Apoprotein A1 and A-II levels between the diabetic and non diabetic subjects.

Aims & Objectives

AIMS AND OBJECTIVES

To do the extended lipid lipoprotein profile and study the commonly associated lipoprotein abnormalities in newly diagnosed diabetes mellitus and hypertensive patients.

Material & Methods

MATERIAL AND METHODS

The present study was conducted in the department of Medicine, MLB Medical College, Jhansi on subjects attending the diabetes clinic, Hypertensive clinic as well as the general medicine OPD and on the patients admitted in the wards.

Criteria for selection :

Any individual who was diagnosed to be having type 2 diabetes mellitus for the first time (within 3 months of diagnosis) was included in the study. The criteria for diagnosing diabetes were the same as laid down by WHO.

Symptoms of diabetes plus RBS ≥ 200 mg%

or

Fasting plasma glucose ≥ 126 mg%

or

2 hours plasma glucose ≥ 126 mg% during an oral glucose tolerance test.

Any individual who was diagnosed to be having systemic hypertension for the first time (within 3 months of diagnosis) was included in the study.

The criteria for diagnosis systemic hypertension were the same as laid down by JNC VII.

A blood pressure recording of more than 140/90 mm of Hg in a related comfortable position of the patient was taken as hypertension.

Exclusion criteria :

- Patients with other associated severe medical or surgical problems.
- Psychiatrically unstable patients.
- Patients already taking same hypolipidemic medications.
- Patients taking medications which alter lipid profile.
- Patients with associated renal and hepatic impairment.
- Patents taking acohol.

Blood glucose measurement : Though it would be ideal to measure venous plasma glucose on each visit of the patient in diabetic clinic but it was very time consuming and costly affair for

the patients. Measurement of blood glucose by glucometer was very convenient, easy, rapid and cheap method as well as quite reliable. So usually blood glucose monitoring was done with the glucometer.

Sampling of blood for extended lipid lipoprotein profile :

Blood samples were taken after an overnight fast of 8 to 12 hours, in the recumbent posture, from anticubital vein without producing any venous stasis. Plasma from the samples were taken out within half an hour of sample withdrawal by centrifugation method. Lipid lipoprotein profile of these samples were analysed by thyrocare center.

Following parameters were analysed in extended lipid lipoprotein profile :-

i) Total cholesterol

ii) HDL cholesterol- Direct

iii) LDL – cholesterol

iv) Triglycerides

v) VLDL cholesterol

vi) LDL/HDL ratio

vii) TC-HDL cholesterol

viii) Apolipoprotein A1 (Apo-A1)

ix) Apolipoprotein B (Apo-B)

x) Lipoprotein (a) [Lp(a)]

Standard lipid profile estimation was done by fully automated biochemistry analyzer. Apo A1, Apo-B and lipoprtein (a) estimation was done by fully automated BN-100 Nephelometry system.

The values given below were followed to label any subject as having abnormal/ normal.

Extended lipid lipoprotein profile values :

Lipid / lipoprotein	Normal range
Total cholesterol	125 - 200 mg%
HDL-cholesterol	Male < 30mg% Female < 50mg%
LDL-cholesterol	85 – 130
Triglycerides	25 – 150
VLDL cholesterol	5 – 40
TC/HDL ratio	< 3 low risk 3 to 5 Avg risk > 5 High risk
LDL/HDL ratio	1.5 – 3.5
Apolipoprotein – A1 (Apo-A1)	Adult – 115 – 210 Male – 110 – 205 Female – 125 – 215
Apolipoprotein-B (Apo-B)	Adult – 55 – 135 Male – 55 – 140 Female – 55 – 125
Lipoprotein (a) (Lp(a))	Adult - < 30

Observations

OBSERVATION

NEWLY DIAGNOSED DIABETIC

Table – I Showing distribution of patients according to sex

	No.	Percentage
Males	11	55
Females	9	45

Table – II Showing distribution of patients according to their age at the time of presentation

	No.	Percentage
25 – 29	3	15
30 – 39	3	15
40 – 49	6	30
50 – 59	4	20
60 – 70	4	20

Table – III Showing distribution of patients according to their HDL-cholesterol levels (in mg%) in females

	No.	Percentage
< 50	7	77.77
> 50	2	22.22

Table – IV Showing distribution of patients according to their HDL- cholesterol levels (in mg%) in males

	No.	Percentage
< 40	11	100
> 40	0	00

Table – V Showing distribution of patients according to their LDL-C levels (in mg%)

	No.	Percentage
< 100	8	40
100 – 129	9	45
130 – 159	3	15
160 – 189	0	00
> 190	0	00

Table – VI Showing distribution of patients according to their Total cholesterol levels (in mg%)

	No.	Percentage
< 200	14	70
200 – 239	5	25
≥ 240	1	5

Table–VII Showing distribution of patients according to their triglyceride levels (in mg%)

	No.	Percentage
< 150	2	10
150 – 199	10	50
200 – 499	7	35
> 500	1	5

Table–VIII Showing distribution of patients according to their VLDL- cholesterol levels (in mg%)

	No.	Percentage
< 40	12	60
≥ 40	8	40

Table – IX Showing distribution of patients according to their Apolipoprotein A1 levels (in mg%)

	No.	Percentage
< 115	19	95
115 – 210	1	5
> 210	0	00

Table – X Showing distribution of patients according to their Apolipoprotein –B levels (in mg%)

	No.	Percentage
< 55	7	35
55 – 135	13	65
> 135	0	00

Table – XI Showing distribution of patients according to their Lipoprotein (a) levels (in mg%)

	No.	Percentage
< 30	15	75
> 30	5	25

Table - III
Distribution of patients according to their HDL-C levels (in mg%) in Females

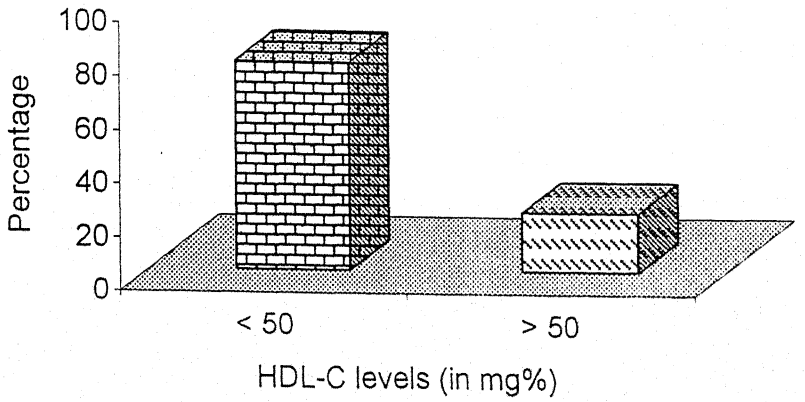


Table - IV
Distribution of Patients according to their HDL-C levels (in mg%) in Males

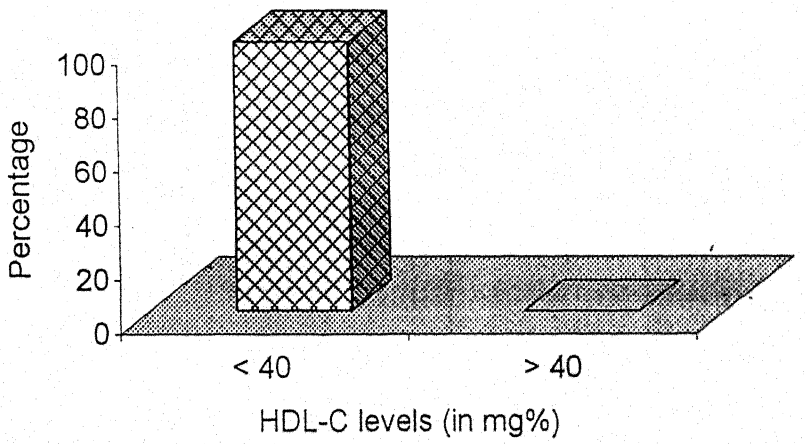


Table - V
Distribution of patients according to their LDL-C levels (in mg%)

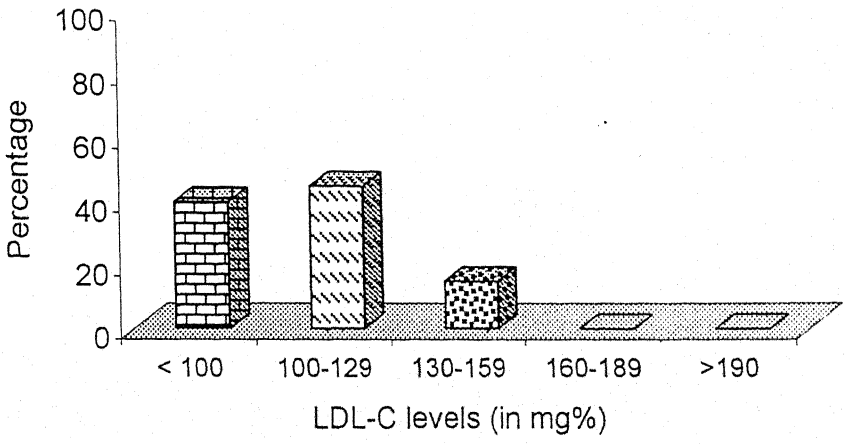


Table - VI
Distribution of Patients according to their Total cholesterol levels (in mg%)

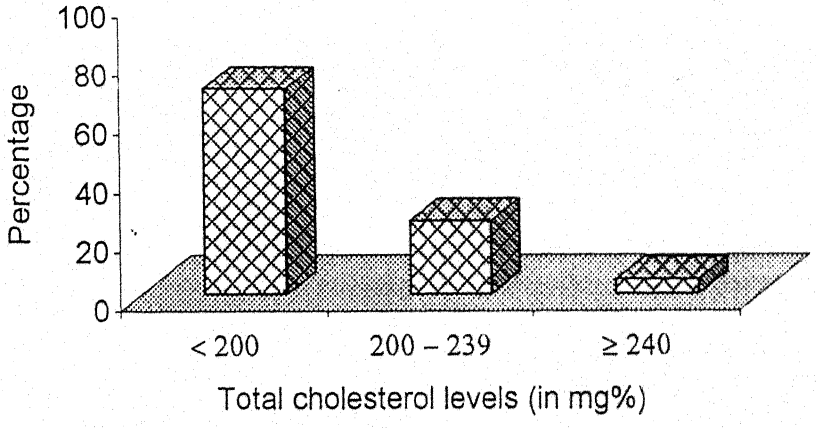


Table - VII
Distribution of patients according to their triglyceride levels (in mg%)

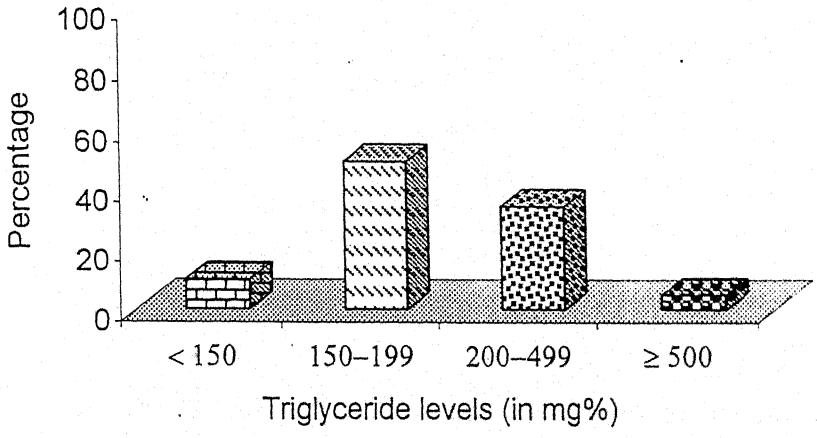


Table - IX
Distribution of Patients according to their Apolipoprotein A1 levels (in mg%)

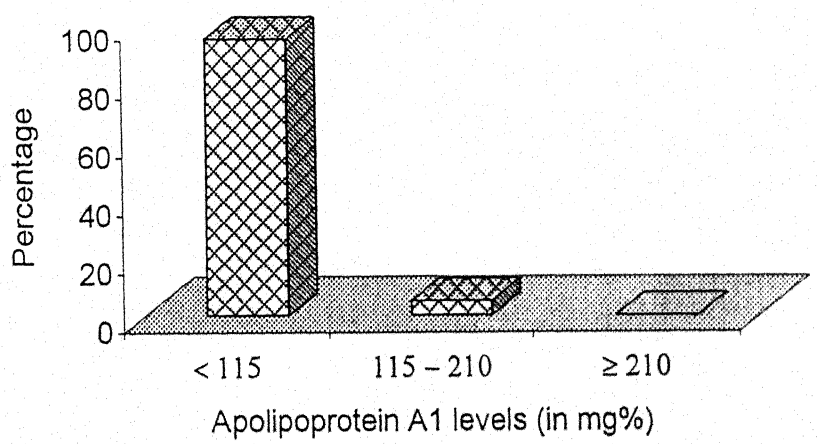


Table - X
Distribution of patients according to their Apolipoprotein -B levels (in mg%)

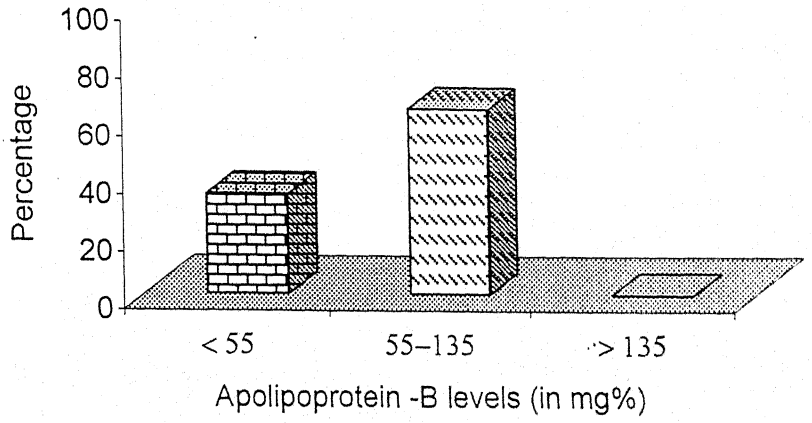
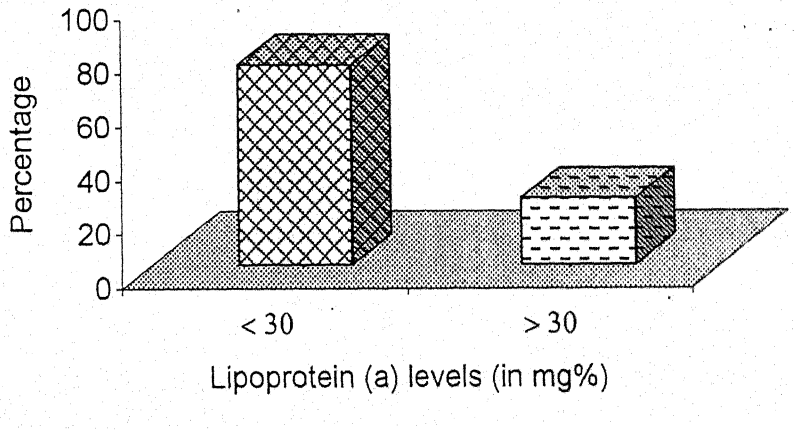


Table - XI
Distribution of Patients according to their Lipoprotein (a) levels (in mg%)



NEWLY DIAGNOSED HYPERTENSIVE

Table – I Showing distribution of patients according to sex

	No.	Percentage
Males	12	60
Females	8	40

Table – II Showing distribution of patients according to their age at the time of presentation

	No.	Percentage
30 – 39	2	10
40 – 49	7	35
50 – 59	6	30
60 – 70	5	25

Table – III Showing distribution of patients according to their STC levels (in mg%)

	No.	Percentage
< 200	8	40
200 – 239	9	45
≥ 240	3	15

Table – IV Showing distribution of patients according to their Triglyceride levels (in mg%)

	No.	Percentage
< 150	2	10
150 – 199	9	45
200 – 499	9	45
≥ 500	0	00

Table – V Showing distribution of patients according to their HDL-C levels (in mg%) in males

	No.	Percentage
< 40	1	8.33
> 40	11	91.66

Table – VI Showing distribution of patients according to their HDL-C levels (in mg%) in Females

	No.	Percentage
< 50	6	75
> 50	2	25

Table–VII Showing distribution of patients according to their LDL- C levels (in mg%)

	No.	Percentage
< 100	1	5
100 – 129	10	50
130 – 159	9	45
160 - 189	0	00
≥ 190	0	00

Table–VIII Showing distribution of patients according to their Apo-A1 levels (in mg%)

	No.	Percentage
< 115	19	95
115 – 210	1	5
> 210	0	00

Table – IX Showing distribution of patients according to their Apo - B levels (in mg%)

	No.	Percentage
< 55	0	00
55 – 135	20	100
> 135	0	00

Table – X Showing distribution of patients according to their Lp(a) levels (in mg%)

	No.	Percentage
< 30	18	90
> 30	2	10

Table - III
Distribution of patients according to their STC levels (in mg%)

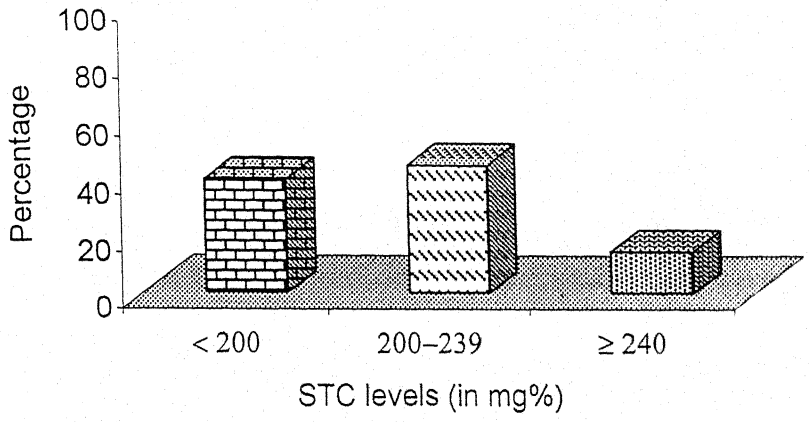


Table - IV
Distribution of patients according to their Triglyceride levels (in mg%)

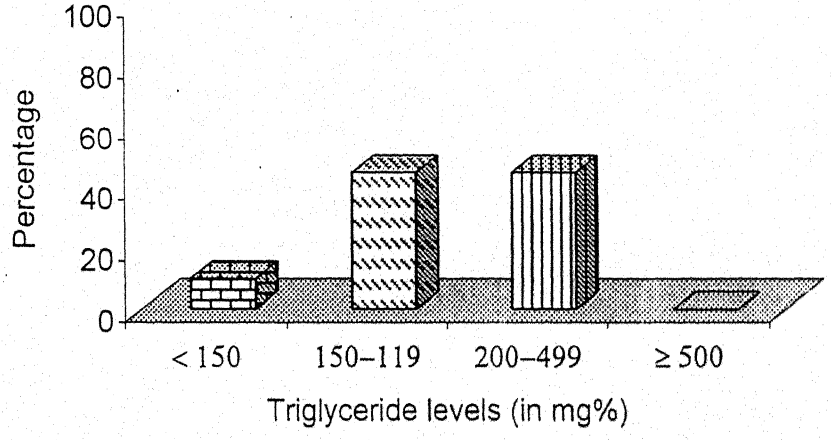


Table - V
Distribution of Patients according to their HDL-C levels in males (in mg%)

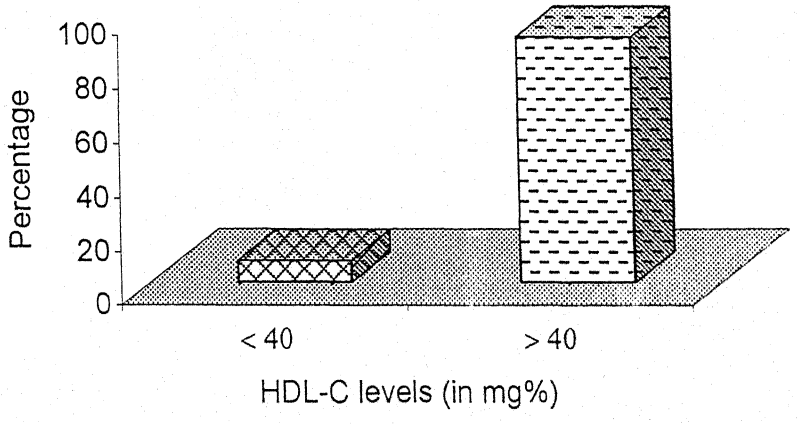


Table - VI
Distribution of Patients according to their HDL-Cholesterol levels in females (in mg%)

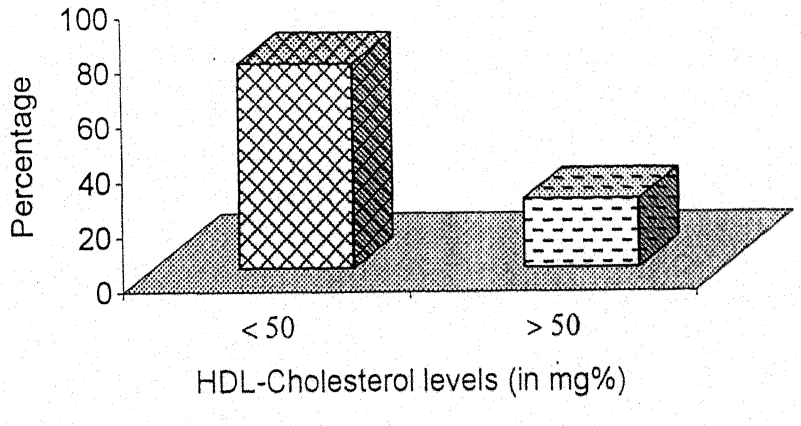


Table - VIII
Distribution of patients according to their Apo-A1 levels (in mg%)

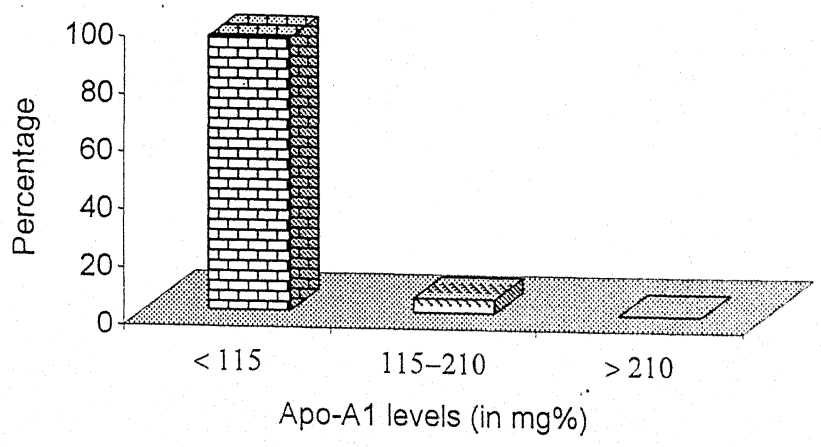
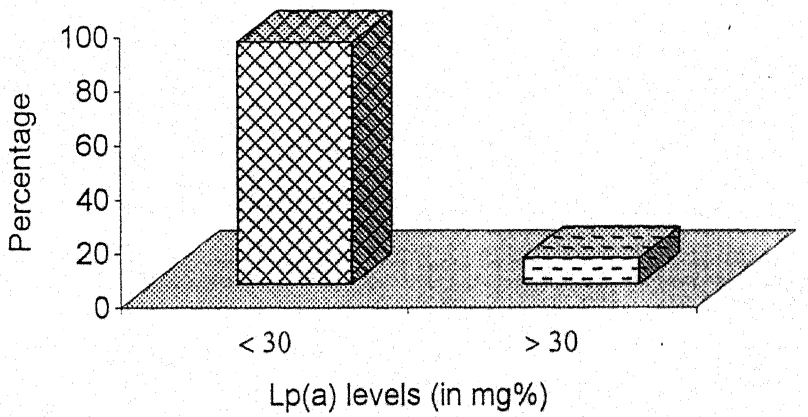


Table - X
Distribution of Patients according to their Lp(a) levels (in mg%)



Discussion

DISCUSSION

The present study was conducted in the department of medicine, M.L.B. Medical College, Jhansi. The subjects were taken from the diabetes OPD, Hypertensive OPD, Medicine General OPD and those who were admitted to wards. The study included 20 patients with type 2 diabetes and 20 patients with essential hypertension detected within 3 months. The study was conducted form Sept. 2004 to Oct. 2005.

Newly Diagnosed Diabetics :

Of the 20 patients studied 11 were males and 9 were females (table I). Maximum number of patients (30%) were in the 40-49 year age group followed by 20% each in the 50-59 age group and 60-69 group (table II). 15% patients were less than30 years of age.

In this study 77.77% females had their HDL-C < 50 and 100% males had their HDL-C < 40 (Table III and IV). So in both groups HDL-C levels were lower. This is consistent with as observed by Garg et al and Stern MP et al and Uvsitupa et al.

Table V shows that nearly 85% of the patients had their LDL-C levels in the range of 100-130 mg% (according ATP-3 guideline values were between optimal to near optimal). Only 15% patients had value > 130 mg%. This is consistent with AM Wagner et al study in which 75% had normocholesterolemia.

Table VI shows that 70% of patients had their cholesterol levels < 200 mg% only 30% had their total cholesterol levels > 200 mg%.

The finding were in accordance with that of Stern MP et al and diabetic control and Complications Trial Research and AM Wagner et al, as they also noted that there was no change in STC levels in diabetes mellitus. But this finding contradicts the findings of Garg et al who found that there was an increase in STC levels in diabetes mellitus.

Table VII shows that only 10% patients had their triglyceride levels below 150 and 50% patients had their triglyceride levels in the range of 150-199 mg% calling for therapeutic life style changes and nearly 40% patients had their TG levels more than 200mg% which required initiation of drug therapy. This finding seems to be consistent with fact that diabetes causes raised triglyceride levels.

Krahulec B et al found hypertriglyceridemia in 66% patients. The finding was also in accordance with MUusitupa et al study as they found that the serum total cholesterol levels in diabetic and non diabetic subjects were similar, but the HDL-C levels were lower and serum triglyceride levels higher in the diabetic than in non diabetic subjects.

Table VIII shows that 60% patients had their VLDL-C values < 40 and 40% had their values < 40, this shows that their was not any significant change in VLDL-C values in diabetic subjects.

Table IX shows that 95% patients had their Apolipoprotein A1 level less than desirable level of 115 mg%. The finding was in accordance with study carried out by Goran Wallidus et al.

Table X shows that 35% patients had their apolipoprotein B levels below desirable level an 65% had their values in desirable range. No one had higher values. This finding contradict the finding of AM Wagner et al who found hyper apo-B in almost half of the normocholesterolemic type 2 diabetic patients.

Table XI shows that 75% patients had their Lp(a) values below normal (< 30 mg%) and only 25% had their values above normal (> 30 mg%). Out of five patients who had raised Lp(a)

levels, three patients had myocardial infarction and one had stroke. This finding consistent with V Mohan et al study that Lp(a) levels were significantly higher in diabetic patients with CAD compared with diabetic patients without CAD. This finding also consistent with SM Haffner study that Lp(a) concentrations in diabetics are not elevated.

Newly Diagnosed Hypetensive :

Of the 20 patients studied 12 were males and 8 were females (Table I). Maximum number of patients (35%) were 40-49 years age group followed by 30%in the 50-59 group (Table II), followed by 25% in the 60-70 group. Only 2 patients were below 30 years.

Table III shows that 60% patients had their serum total cholesterol value above 200 and 40% had below 200. This is consistent with several well conducted studies that have demonstrated that cholesterol levels are significantly higher in hypertensive patients.

Table IV shows that 45% patients had their triglyceride levels in range of 150-199 and 45% had in range of 200-499. So nearly 90% patients had their triglyceride levels >150 mg%. This

consistent with studies that hypertriglyceridemia commonly present in hypertensive patients.

Table V shows that more than 90% hypertensive males had their HDL-C >40 mg%.

Table VI shows that nearly 75% hypertensive females had their HDL-C levels below 50 mg%. This shows that HDL-C values are more deranged in females than males in hypertensive patients.

Table VIII shows that hypertensive patients had significantly lower values of Apo-A1. But Apo-B values (Table IX) were normal in nearly 100% patients.

There was also not any significant derangement in Lp(a) (Table X) values in hypertensive patients.

Several well conducted epidemiological studies have demonstrated that cholesterol levels are significantly higher in hypertensive patients than in Age, Sex and Body mass index match normotensive patients. Our study also indicate significant incidence of hypercholesterolemia in these patients. The association of high blood pressure and dyslipedmia is so common that many have argues that the high blood pressure it self may play a role in altering lipid metabolism in such that to result in

hypercholetserolemia, hypertriglyceridemia and low levels of HDL cholesterol. But recent data, suggest that high blood pressure and dyslipidemia are independent variables that present clinically at different times.

Although hyperlipidemia and high blood pressure are independently important risk factors, the likelihood of coronary events appears to be increased when the two problems occurs together. Regardless of the cause of accelerated atherosclerosis in patients with concomitant lipid and blood pressure abnormalities, there are important therapeutic implications. Studies using coronary events as the end point of treatment for hypertensive patients have shown that treatment of high blood pressure alone or dyslipidemia alone produces only modest results. Only when both problems are controlled is there a marked reduction in coronary events.

Conclusion

CONCLUSIONS

Conclusions that can be drawn from the present study in newly diagnosed diabetics are :

1. At the time of diagnosis in patients of new onset diabetes most patients had deranged lipid lipoprotein profile.

2. Nearly 75% of female and almost all males had below normal HDL-C levels.

3. Nearly 90% of patients had their triglyceride levels above normal (>150 mg%).

4. 70% of patients had normal total cholesterol value (<200mg%) and only 5% patients were found to have total cholesterol levels greater than 240 mg%.

5. Only 45% patients had LDL levels in optimal level.

6. Nearly 95% patients had subnormal Apolipoprotien A1 levels (<115 mg%).

7. No patients was found in the present study to have increased apolipoprotein B (65% had normal value and 35% had subnormal values).

8. 75% of patient had normal lipoprotein (a) levels and in 25% patients whom Lp(a) levels were increased had increased incidence of coronary heart disease.

Conclusions that can be drawn from the present study in newly diagnosed hypertensive patients are :

1. At the time of diagnosis in patients of new onset essential hypertension, most patient had deranged lipid lipoprotein profile.

2. 60% of patients had their total cholesterol values above normal and 40% had values below normal.

3. 90% of patients had their triglyceride levels above normal (>150 mg%).

4. Nearly 90% males and 25% of females had their triglyceride levels above normal.

5. 95% patients had their LDL-C levels in near optimal and high range (50 and 45%).

6. 95% patients had their Apolipoprotein A1 value in subnormal range (<115 mg%).

7. Nearly all the patients had their Apolipoprotein B value in normal range.

8. Nearly all the patients had their lipoprotein (a) values in normal range.

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Master Chart

NEWLY DIAGNOSED DIABETIC

No.	Name	Age/Sex	STC	HDL-C	LDL-C	VLDL-C	Triglyceride	LDL/HDL Ratio	STC/HDL-C Ratio	Apo-A1	Apo-B	Lp(a
1.	Deepak Gupta	45/M	114	36	65	13	65	1.81	3.17	99	45	14.0
2.	Prem Narayan	50/M	141	36	57	47.60	238	1.58	3.92	88	62	74
3.	Atar Singh	55/M	101	35	30	35.86	179.30	0.86	2.89	63	45	39.4
4.	Mahesh	45/M	222	31	-	282.80	1414	-	7.16	73	73	11.0
5.	Maradeen	46/M	111	35	38	37.84	189.20	1.09	3.17	54	52	10.5
6.	Sachin Gupta	25/M	168.78	37	101	30.36	151.80	2.73	4.56	54	62	17.87
7.	Ghanshyam Das	65/M	138.60	36	70	32.76	163.80	1.94	3.85	61	69	10.5
8.	Ram Kumar	25/M	140	25	64	50.58	252.90	2.56	5.60	40	80	28.36
9.	Tejram	45/M	129.15	25	36	68.02	340.10	1.44	5.17	61	54	18.90
10.	Anja	50/F	240	48	155	37	187	3.22	5.00	70	56	24.40
11.	Argun Ram	40/M	160	32	96	32	160	3.00	5.00	54	46	22.01
12.	Leelawati	25/F	150	38	106	33	185	2.78	3.94	56	44	20.10
13.	Sheela	35/F	210	45	133	32	160	2.95	4.66	50	54	15.80
14.	Kiran	45/F	217	45	121	41	208	2.68	4.82	52	62	16.40
15.	Kamlesh Singh	30/M	170	36	100	34	173	2.77	4.72	44	52	24.40
16.	Munni Devi	50/F	233	55	122	56	280	2.21	4.23	88	45	35.40
17.	Kishori Devi	70/F	213	45	126	42	213	2.8	4.73	70	62	21.22
18.	Baini Bai	70/F	189	45	102	42	210	2.26	4.2	56	55	24.24
19.	Naznee Begam	39/F	180	43	108	30.20	151	2.48	4.19	117	67	50.25
20.	Mankunwar	60/F	188	56	105	26.80	134	1.88	3.36	112	92	49.53

NEWLY DIAGNOSED HYPERTENSIVE

S.No.	Name	Age/Sex	STC	TG	HDL	LDL	VLDL	LDL/HDL Ratio	T. Choles /HDL Ratio	Apo-A1	Apo-B	Lp(a)
1.	Shobhan	70/F	192	136	54	110	28	2:1	3.55	110	82	12.3
2.	Saraswati	42/F	190	160	40	118	32	2.9:1	4.75	102	78	10.3
3.	Munnalal	52/M	220	213	46	132	42	2.8:1	4.78	90	59	9.45
4.	Mankunwar	60/F	188	134	56	105	26.80	1.88:1	3.36	112	92	49.53
5.	Manjis	47/F	185	193	48	157	32	3.2:1	3.85	100	98	19.6
6.	Mrs. Sharda	40/F	216	166	46	137	33	2.9:1	4.69	100	66	12.7
7.	Munnalal	40/M	220	213	46	132	42	2.8:1	4.78	110	118	16
8.	Munnalal	55/M	237	160	48	157	32	3.2:1	4.93	92	98	18
9.	Shikar chandra	50/M	214	160	46	136	32	2.9:1	4.65	89	104	23
10.	Kamlesh	45/M	248	200	56	152	40	2.7:1	4.42	115	95	18.50
11.	Utpal Rastogi	36/M	256	360	56	128	72	2.2:1	4.57	90	85	19.40
12.	Rameshwar	55/M	200	200	44	116	40	2.6:1	4.54	104	92	12.4
13.	Shivdayal	60/M	176	160	38	104	32	2.6:1	4.4	90	104	19.6
14.	Prakash	45/M	232	200	48	144	40	3:1	4.83	99	108	36
15.	Maya	50/F	144	153	36	78	30	2.1:1	4	95	88	18
16.	Ramesh Chandra	62/M	216	200	44	132	40	3:1	4.90	92	70	17.6
17.	Meena	40/F	184	166	42	109	33	2.5:1	4.38	98	68	22
18.	Amarwati	60/F	200	173	42	124	34	2.9:1	4.76	100	92	24
19.	Parveen	35/F	208	205	40	127	41	3.1:1	5.2	92	68	10.7
20.	GL Verma	55/M	192	186	44	111	37	2.5:1	4.36	99	104	17.6